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HELLER EHRMAN WHITE & MCAULIFFE LLP
1717 RHODE ISLAND AVE, NW
WASHINGTON, DC 20036-3001

| EXAMINER | |
|---|---|
| STEELE, AMBER D | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/658,752 | LOHNING, CORINNA | |
| | Examiner | Art Unit | |
| | Amber D. Steele | 1639 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *17-23* is/are pending in the application.

4a) Of the above claim(s) *23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 September 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9-10-2003*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20050830*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Claims*

1. Claims 17-23 are currently pending.

Claims 1-16 and 24-31 were canceled by the Applicant in the Amendment received on December 10, 2003.

### *Election/Restrictions*

2. Applicant's election with traverse of Group I (claims 17, 19, and 22) in the reply filed on November 28, 2005 is acknowledged. The traversal is on the ground(s) that claims 17-22 can be examined without undue burden on the Examiner and because claims 18-22 all depend from claim 17. Therefore, if claim 17 is found novel and non-obvious over the prior art then claims 18-22 must *a priori* be novel and non-obvious. Due to the amendment to claim 18 and Applicant's arguments, claims 18 (previous Group II) and 20-21 (previous Group III) will be rejoined with Group I for examination purposes.

In addition, the restriction of Group IV (claim 23) was not traversed.

3. Claim 23 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 28, 2005.

4. Applicant's election without traverse of gene III protein with an additional methionine residue as the species of modified wild type protein, five histidines and one cysteine as the species of one to six additional amino acid residues, an expression vector encoding $V_H$-$C_H$ and

$V_L$-$C_L$ as the species of vector, and *E. coli* as the species of host cell in the reply filed on November 28, 2005 is acknowledged.

***Information Disclosure Statement***

5. The information disclosure statement filed September 10, 2003 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Applicant stated that WO 94/00588 and WO 97/40141 could be found in the parent application (09/809,517). However, copies of the documents were not found in U.S. Patent Application 09/809,517.

***Drawings***

6. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: Figures 8A, 8B, 9A, and 9B are not described in the specification. Corrected drawing sheets in compliance with 37 CFR 1.121(d), **or amendment to the specification to add the reference character(s) in the description** in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and

informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

7. The drawings/figures are objected to because tables and sequence listings included in the specification must not be duplicated in the drawings. See 37 CFR §1.58(a) and §1.83(a). Applicants are advised that upon issuance of a patent, the complete text of the sequence listing submitted in compliance with 37 CFR §§1.821-1.825 will be published as part of the patent. Applicants should amend the specification to delete any figures/drawings which consist only of nucleic acid or protein sequences which have been submitted in their entirety in computer readable format (e.g. as SEQ ID Nos) and should further amend the specification accordingly to reflect the replacement of the drawing/figure by the appropriate SEQ ID No.

Appropriate correction is required.

***Specification***

8. The disclosure is objected to because of the following informalities: In the first line of the specification, the following corrections should be made: U.S. Patent Application 09/809,517 is now U.S. Patent 6,753,136 which is a continuation of PCT/EP00/06968 7-20-00. Also, the dates for the foreign priority documents should be provided.

Appropriate correction is required.

***Claim Interpretation***

9. The presently claimed invention is drawn to a nucleic acid sequence, a vector, and a host cell wherein the nucleic acid sequence encodes a modified variant coat protein of a bacteriophage and between one and six additional amino acids where one of the amino acids is a

cysteine. In addition, the nucleic acid sequence and/or vector can further encode a peptide sequence, an additional cysteine residue, and/or an immunoglobulin or immunoglobulin fragment.

***Claim Rejections - 35 USC § 112***

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 17-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **written description** rejection.

12. With regard to the written description requirement, the attention of the Applicant is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)] (the case is referred to herein as "*Lilly*").

Additionally, it is noted that written description is legally distinct from enablement: "Although the two concepts are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co.*

Although directed to DNA compounds, this *Eli Lilly* holding would be deemed to be applicable to any compound or a generic of compounds; which requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the compound or generic(s). In this regard, applicant is further referred to *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997); "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001); and *Univ. Of Rochester v G. D. Searle and Co.* 249 F. Supp. 2d 216 (W.D.N.Y. 2003) affirmed by the CAFC on February 13, 2004 (03-1304) publication pending.

Additionally, *Lilly* sets forth a two part test for written description:

A description of a genus of cDNA's may be achieved by means of a recitation of: a representative number of cDNA's, defined by nucleotide sequence, falling within the scope of the genus OR of a recitation of structural features common to the members of the genus. See *Regents of the University of California v. Eli Lilly & Co.* 119 F.3d 1559 (Fed. Cir. 1997) at 1569.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Additionally, Cf. University of Rochester v G.D. Searle & Co., Inc., Monsanto Company, Pharmacia Corporation, and Pfizer Inc., No. 03-1304, 2004 WL 260813 (Fed. Cir., Feb. 13, 2004) held that:

> *Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.*

13. In the present instance, the specification discloses only limited examples (e.g. Examples 1-2; page 6 describing five wild type coat proteins and page 11 describing four tags or additional amino acids; and Table 2 describing five scFvs or F(ab)s, Tables 3-4 describing five cysteine modified coat proteins, and Table 6 describing cysteine modified F(ab)s) that are not representative of the claimed genus of a nucleic acid sequence encoding a "modified variant of a wild type coat protein of a bacteriophage" and "one or more peptide sequences"; nor do the claims recite sufficient structural feature(s) which is(are) common to members of the genus

sufficient to demonstrate possession of the genus. The instant claims are drawn to a nucleic acid sequence encoding a "modified variant of a wild type coat protein of a bacteriophage" and "one or more peptide sequences", a vector comprising the nucleic acid, and a host cell comprising the nucleic acid sequence. The claimed nucleic acid sequence encoding a "modified variant of a wild type coat protein of a bacteriophage" is only defined by functional properties (e.g. "causes or allows the incorporation of the coat protein into the phage coat"). In addition, the nucleic acid sequence further encoding "one or more peptide sequences" is only defined by functional properties (e.g. "for purification and/or detection purposes". The CAFC held that a functional definition is insufficient to adequately describe a product, therefore, an adequate written description not based on a functional definition is necessary.

The Examiner further notes the present claims stated by Applicant are broader in scope that those that were held to be impermissible in *Lilly* because, unlike *Lilly*, Applicants' claims encompass a vast number of nucleic acid sequence encoding a "modified variant of a wild type coat protein of a bacteriophage" and "one or more peptide sequences". Here, the Applicant claims a nucleic acid sequence encoding a "modified variant of a wild type coat protein of a bacteriophage" (please refer to claim 17) and "one or more peptide sequences" (please refer to claim 18). The scope of these claims include a vast number of sequences because while the claims place a limit on the number of additional components (e.g. between one and six amino acid residues), the claims do not place a limit on the number of components (e.g. nucleic acids) of the modified wild type coat protein which can be a full length wild type coat protein or "one or more parts" of the wild type coat protein including deletions and/or truncated coat protein (see pages 6-7 of the Specification) or of the "peptide sequences" (e.g. detection tag/five histidines, c-

yc, FLAG, or Strep-tag on pages 7 and 11 of the specification). In addition, the claims do not specify the type of components excluding the necessary cysteine residue (e.g. any amino acid residue including the 20 naturally occurring residues or synthetic/altered amino acids or any wild type coat protein of any bacteriophage while the specification only provides wild type coat proteins of filamentous phage including pIII, pVI, pVII, pVIII, and pIX; please refer to pages 6 and 11 of the specification). Furthermore, the specification and claims do not place any limit on the number of components (e.g. one or more "parts" of the wild type coat protein or one or more peptide sequences), the types of components, or the manner in which the components might be connected to "cause or allow incorporation of the coat protein into the phage coat" or "for purification and/or detection purposes" (e.g. location of the cysteines relative to the coat protein; please refer to pages 8 and 10 of the Specification wherein the "cysteine is present at or in the vicinity of the C- or N-terminus" or "the cysteine may link two parts of the coat protein"). Therefore, Applicant is using an inadequately described components (e.g. "one or more parts of a wild type coat protein of a bacteriophage" and "one or more peptide sequences") to inadequately describe the claimed nucleic acid sequence encoding a "modified variant of a wild type coat protein of a bacteriophage" and "one or more peptide sequences". In addition, the "causes or allows" claim language (e.g. claim 17) further exacerbates this problem because the conditions under which the "one or more parts of a wild type coat protein of a bacteriophage" will "cause or allow" the "incorporation of the coat protein into the phage coat" are not specified. Consequently, there is no teaching that would allow a person of skill in the art to determine *a priori* that the Applicant was in possession of the full scope of the claimed invention at the time of filing because there is no common structural attributes that can link together all of the claimed

"nucleic acid sequence encoding a modified variant of a wild type coat protein of a bacteriophage".

Moreover, the vector further comprising additional nucleic acid sequences encoding a polypeptide or protein comprising an immunoglobulin or a functional fragment (e.g. present claims 20-21) is not adequately described. The scope of these claims include a vast number of sequences because while the claims or the specification do not place a limit on the number of components (e.g. nucleic acids/amino acids) of the immunoglobulin or functional fragment. In addition, the claims do not specify the type of components excluding the necessary two cysteine residues (e.g. any immunoglobulin or fragment including full length antibody, scFv, Fab, $F(ab)_2$, $V_L$, $V_H$, etc.; please refer to pages 10 and 12 of the specification). Furthermore, the specification and claims do not place any limit on the number of components (e.g. "fragments"), the types of components, or the manner in which the components might be connected to form a "functional" fragment. Therefore, Applicant is using inadequately described components (e.g. polypeptide, protein, immunoglobulin, fragment) to inadequately describe the claimed vector. In addition, the "functional" claim language (e.g. claim 21) further exacerbates this problem because the conditions under which the "immunoglobulin fragment" will be "functional" are not specified (e.g. does "functional" antigen-binding refer to a specific kd value or range?). Consequently, there is no teaching that would allow a person of skill in the art to determine *a priori* that the Applicant was in possession of the full scope of the claimed invention at the time of filing because there is no common structural attributes that can link together all of the claimed vectors comprising one or more additional nucleic acid sequences encoding a polypeptide or protein including immunoglobulin or immunoglobulin fragments.

While the general knowledge and level of skill in the art for making nucleic acid sequences encoding modified proteins and various expression vectors including phage display vectors is high, this knowledge and level of skill does not supplement the omitted description because specific, not general, guidance is needed for the nucleic acid sequence encoding a "modified variant of a wild type coat protein of a bacteriophage" and "one or more peptide sequences" and the vector comprising nucleic acid sequences encoding polypeptide or protein. Since the disclosure fails to describe the common attributes or characteristics that identify all of the members of the genus or even a substantial portion thereof, and because the genus is vast and highly variant [(e.g. any nucleic acid sequence encoding one or more parts of a full length or truncated coat protein (e.g. conservatively hundreds of combinations) with any naturally or synthetic amino acid residues (e.g. conservatively hundreds of combinations) and any peptide sequences (e.g. conservatively billions) in any vector (e.g. conservatively hundreds) further comprising nucleic acid sequences encoding any polypeptide or protein (e.g. conservatively billions) including any immunoglobulin or immunoglobulin fragment (e.g. conservatively billions)], the limited examples in the specification (please refer to Examples 1-2) are insufficient to teach the entire genus.

The specification discloses only limited examples that are not representative of the claimed genus of a nucleic acid sequence encoding a "modified variant of a wild type coat protein of a bacteriophage" and "one or more peptide sequences" or a vector comprising nucleic acid sequences encoding polypeptide or protein; nor do the claims recite sufficient structural feature(s) which is(are) common to members of the genus sufficient to demonstrate possession of the genus. The specification lists five wild type coat proteins (please refer to page 6 of the

specification), one core vector (e.g. pMorph; please refer to Examples 1-2), nonspecific $V_H$ and $V_L$ or $V_H$-$C_H$ and $V_L$-$C_L$ domains as the polypeptide or protein and five specific VH and VL domains (please refer to page 12 and Table 2 of the Specification). In addition, the specification only provides five cysteine modified coat proteins (Tables 3-4). Therefore, the teachings in the specification are general teachings relating without guidance as to the individual components of the product. The expedient statements in the specification do not relate to an adequate disclosure or how to make and use the claimed invention. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to adequately describe the vast genus. Thus, Applicant does not appear to be in possession of the claimed genus.

***Claim Rejections - 35 USC § 102***

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 17-20, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Kay et al. U.S. Patent 5,747,334 issued May 5, 1998.

Kay et al. teach nucleic acid sequences for binding molecules (e.g. TSARs) with additional invariant residues including cysteine residues to form a disulfide bond (please refer to column 6, lines 28-67). Figures 1D and 1E of Kay et al. depict M13 gene III fused with invariant residues encoding 2-4 cysteines wherein the entire invariant nucleotide sequence contains 6, 9, or 12 nucleotides or 2, 3, or 4 amino acids, but can also include longer sequences (e.g. present claim 17; please refer to column 15, lines 53-67; column 16, lines 1-15; column 19, lines 30-67; and column 20, lines 1-64). Figure 2 of Kay et al. teach the addition of c-myc to gene III (e.g. peptide sequence of present claim 18; please refer to Figure 2). In addition, Kay et al. teach peptide libraries encoded by nucleic acids encoding gene III and cysteine residues constructed in M13 phage-display vectors and introduced into a host cell including *E. coli* (e.g. present claims 19 and 22; please refer to column 1, lines 51-67; column 2, lines 1-43; and sections 5.1.2-5.1.3 and 6.1.2-6.2). Furthermore, Kay et al. teach that more than one cysteine residue may be present in the vector (e.g. present claim 20; please refer to column 19, lines 30-67; column 20, lines 1-67; and column 43, lines 7-30). Therefore, one of ordinary skill in the art would have anticipated the presently claimed invention of claims 17-20, and 22 in view of the teachings of Kay et al.

16. Claims 17-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Deem et al. U.S. Patent 6,341,256 B1 filed March 31, 1995.

Deem et al. teach nucleic acid sequences of proteins utilized in drug design (please refer to columns 5-6, section 3). Deem et al. teach oligonucleotides encoding two cysteines and being at least 2 amino acids long and fused to M13 gene III protein (e.g. present claims 17-18; please refer to columns 17, lines 5-67; column 18, lines 1-11; and columns 58-59, section 6.3.1). In

addition, Deem et al. teach a nucleic acid sequence encoding methionine, histidine, and two cysteine residues fused to gene III protein (please refer to columns 58-59, section 6.3.1). Additionally, Deem et al. teach phage-display vectors and *E. coli* host cells utilized to express the nucleic acid sequences encoding cysteines and other amino acids (e.g. present claims 19-20 and 22; please refer to column 17, lines 5-67; column 18, lines 1-4; and column 20, lines 6-17). Furthermore, Deem et al. teach that the target molecule utilized for screening can be an antigen or an antibody comprising Fab, Fab', F(ab')2, constant regions, etc. (e.g. VH-CH and VL-CL or immunoglobulin fragment of present claim 21; please refer to column 4, lines 25-40 and column 12, lines 40-67). Moreover, Deem et al. teach methods of expressing proteins via phage display where the proteins are displayed on the phage surface (please refer to column 15, lines 28-44 and 66-67 and column 16, lines 1-23). Therefore, the presently claimed invention of present claims 17-22 would have been anticipated by one of skill in the art in view of Deem et al.

17. Claims 17-19 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Cutler et al. U.S. Patent 6,309,642 B1 filed May 13, 1998.

Cutler et al. teach nucleic acid sequences for mimotopes and vaccine vectors (please refer to column 4, lines 35-48) and phage-displayed mimotopes (please refer to Example 1). Cutler et al. specifically teach a peptide fused to gene III with an added cysteine to facilitate peptide coupling (e.g. present claims 17-18; please refer to Example 4). In addition, Cutler et al. teach phage vectors and E. coli host cells to produce mimotopes (e.g. present claims 19 and 22; please refer to Example 1). Therefore, the presently claimed invention of present claims 17-19 and 22 would have been anticipated by one of skill in the art in view of Cutler et al.

***Claim Rejections - 35 USC § 103***

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al. U.S. Patent 5,747,334 issued May 5, 1998 and Kipriyanov et al. 1994 Molecular Immunology Volume 31 Number 4 pages 1047-1058 "Recombinant single-chain Fv fragments carrying C-terminal cysteine residues: production of bivalent and biotinylated miniantibodies".

Kay et al. teach nucleic acid sequences for binding molecules (e.g. TSARs) with additional invariant residues including cysteine residues to form a disulfide bond (please refer to column 6, lines 28-67). Figures 1D and 1E of Kay et al. depict M13 gene III fused with invariant residues encoding 2-4 cysteines wherein the entire invariant nucleotide sequence contains 6, 9, or 12 nucleotides or 2, 3, or 4 amino acids, but can also include longer sequences (e.g. present claim 17; please refer to column 15, lines 53-67; column 16, lines 1-15; column 19, lines 30-67; and column 20, lines 1-64). Figure 2 of Kay et al. teach the addition of c-myc to gene III (e.g. peptide sequence of present claim 18; please refer to Figure 2). In addition, Kay et al. teach peptide libraries encoded by nucleic acids encoding gene III and cysteine residues constructed in M13 phage-display vectors and introduced into a host cell including *E. coli* (e.g. present claims 19 and 22; please refer to column 1, lines 51-67; column 2, lines 1-43; and sections 5.1.2-5.1.3 and 6.1.2-6.2). Furthermore, Kay et al. teach that more than one cysteine residue may be present in

the vector (e.g. present claim 20; please refer to column 19, lines 30-67; column 20, lines 1-67; and column 43, lines 7-30).

However, Kay et al. does not specifically teach vectors encoding immunoglobulin or immunoglobulin fragments.

Kipriyanov et al. teach vectors encoding $V_H$ linked to $V_L$ via a (glycine$_4$serine) linker and fused to a c-myc tag with a (cysteine histidine$_5$) C-terminal addition (e.g. present claim 22; please refer to page 1048, Materials and Methods, section *E. coli* strains and plasmids and Figure 1). In addition, Kipriyanov et al. teach that the five histidine residues were added to facilitate isolation of the immunoglobulin fragments (please refer to page 1050, Results, section Vector design for scFv expression). Furthermore, Kipriyanov et al. teach that the C-terminal cysteine residues of Fab' or additional cysteine residues could be useful for coupling reagents to the immunoglobulin fragments (please refer to page 1047-1048, Introduction and page 1054, Results, section Production and characterization of biotinylaed scFv).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the phage-display vectors with one or more cysteine residues taught by Kay et al. with the immunoglobulin fragments taught by Kipriyanov et al.

One having ordinary skill in the art would have been motivated to do this because the TSARs taught in Kay et al. are ligand-binding proteins similar to immunoglobulins or immunoglobulin fragments (please refer to column 4, lines 25-55 and column 8. lines 42-63). Therefore, the methods utilized by Kay et al. to identify binding molecules via phage-display libraries that are reproducible, quick, simple, efficient, and inexpensive would be useful for expressing the immunoglobulins and immunoglobulin fragments taught by Kipriyanov et al. in

phage-display vectors to screen for immunoglobulins or immunoglobulin fragments that bind to specific ligands (please refer to column 6, lines 53-67 and columns 7-9 of Kay et al.).

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the TSARs expressed in phage-display vectors with cysteine residues taught by Kay et al. with the immunoglobulin fragments with a cysteine residue taught by Kipriyanov et al. because the TSARs binding domain is between 20 and 100 amino acid in length and is therefore similar in length to the approximately 120 amino acids of the variable regions of immunoglobulin (please refer to column 7, lines 55-67 and column 8, lines 1-5 and Examples of TSAR libraries taught by Kay et al.). Furthermore, Kay et al. teach that the phage-display vector can be utilized to display immunoglobulins (please refer to column 2, lines 19-35).

Therefore, the combination of the TSARs expressed in a phage-display vectors with cysteine residues modified with the immunoglobulin fragments taught by Kipriyanov et al. render the instant claims 17-22 prima facie obvious.

20. Claims 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cutler et al. U.S. Patent 6,309,642 B1 filed May 13, 1998 and Jespers et al. U.S. Patent 6,017,732 filed September 4, 1997.

Cutler et al. teach nucleic acid sequences for mimotopes and vaccine vectors (please refer to column 4, lines 35-48) and phage-displayed mimotopes (please refer to Example 1). Cutler et al. specifically teach a peptide fused to gene III with an added cysteine to facilitate peptide coupling (e.g. present claims 17-18; please refer to Example 4). In addition, Cutler et al. teach

phage vectors and E. coli host cells to produce mimotopes (e.g. present claims 19 and 22; please refer to Example 1).

However, Cutler et al. does not specifically teach vectors encoding an immunoglobulin or immunoglobulin fragment with an additional cysteine residue.

Jespers et al. teach bacteriophage display libraries utilizing gene III to display cysteine altered immunoglobulins (e.g. present claims 20-21; please refer to Example 1). In addition, Jespers et al. teach that immunogloibulins and immunoglobulin fragments include $V_H$-$V_L$ and $V_H$-$C_H1$ and $V_L$-$C_L$ (please refer to column 3, lines 1-16). Additionally, Jespers et al. teach that cysteine groups may be introduced into more than one site of the immunoglobulin or immunoglobulin fragment (please refer to column 7, lines 20-56). Furthermore, Jespers et al. teaches that cysteine modified immunoglobulin fragments can be displayed on phage via gene III (please refer to Example 1).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the gene III-cysteine phage display vector taught by Cutler et al. with the cysteine-antibody fragment construct taught by Jespers et al.

One having ordinary skill in the art would have been motivated to do this due to the teachings of Jespers et al. stating that incorporating more than one cysteine residue within the same molecule (e.g. gene III fused to $V_L$-$V_H$ would be one molecule) would allow for different reagents to be incorporated (please refer to column 7, lines 20-38). Furthermore, Jespers et al. teaches that the cysteine residue in the VL or VH could be utilized for disulfide bonding between VL and VH to form an antigen-binding fragment while the cysteine residue on another molecule (e.g. gene III) could be utilized for the incorporation of a chemical moiety including fluorescent

for isolation (please refer to column 3, lines 50-67; column 4, lines 1-33; and column 7, lines 20-46).

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the gene III-cysteine phage display vector taught by Cutler et al. with the cysteine-antibody fragment construct in a gene III phage display vector taught by Jespers et al. because of the examples provided by Jespers showing that the cysteine modification of the antibody fragment does not interfere with expression and the examples provided by Cutler et al. showing the cysteine modification of gene III does not interfere with expression (please refer to Examples 1 of Jespers et al. and Example 1 of Cutler et al.).

Therefore, the modification of the gene III-cysteine phage display vector taught by Cutler et al. with the cysteine-antibody fragment construct in a gene III phage display vector taught by Jespers et al. render the instant claims 17-22 prima facie obvious.

***Future Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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ADS
January 9, 2006

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600